

88. An article of manufacture comprising a drug formulation in a sealed vial suitable for administration of a drug to a human subject in need thereof, said formulation comprising at least one protein and drug nanoparticles having a size in the range of about 10 nm up to about 1000 nm.

89. The composition of claim 88 wherein said drug formulation is a dry powder.

90. The composition of claim 88 wherein the drug formulation is a liquid.

91. The composition of claim 88 wherein said drug is hydrophobic.

92. A formulation of paclitaxel suitable for administration to a human subject in need thereof wherein the pharmacokinetics are such that the area under the curve (AUC) for paclitaxel in said formulation is significantly less than the AUC for paclitaxel in TAXOL at the same dose.

93. A formulation of paclitaxel suitable for administration to a human subject in need thereof wherein the pharmacokinetics are such that half-life for paclitaxel in said formulation is significantly higher than the half-life for paclitaxel in TAXOL at the same dose.

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#### REMARKS

In accordance with the present invention, there are provided methods and formulations useful for the *in vivo* delivery of substantially water insoluble pharmacologically active agents (such as the anticancer drug paclitaxel) in which the pharmacologically active agent is delivered in the form of suspended particles coated with protein. The present invention is particularly useful in reducing the toxicity of paclitaxel in a subject in need thereof by eliminating the toxic excipients associated with *in vivo* delivery of paclitaxel.

By the present communication, claims 66-93 have been added and claims 29, 31, 32, 35, and 46-52 have been amended to define Applicants' invention with greater particularity. No new

matter is introduced as all new claim language is fully supported by the specification and original claims. In addition, claims 1-28 and 36-45 have been cancelled. Upon entry of this amendment, claims 29-35, 46-52, and 66-93 will be pending.

The rejection of claims 45, 46, and 48-52 under 35 U.S.C. 102(e) as allegedly being anticipated by Desai, et. al. (U.S. Patent No. 5,916,596) is respectfully traversed. With specific reference to claim 45, the rejection is rendered moot by the cancellation of this claim herein. With specific reference to claims 46 and 48-52, Applicants' invention, as defined for example by claim 46, distinguishes over Desai '596 by requiring a lyophilized formulation of a taxane, e.g., comprising taxane nanoparticles of a well-defined size. While Desai '596 is acknowledged as a significant advance in the art, only the present Application describes lyophilized formulations of paclitaxel comprising paclitaxel nanoparticles of a well-defined size. Accordingly, reconsideration and withdrawal of the rejection of claims 46 and 48-52 under 35 U.S.C. 102(e) are respectfully requested.

The rejection of claims 1-44 and 47 under 35 U.S.C. 103(a) as allegedly being unpatentable over Desai, et. al. in view of Langer, et. al. (*Seminars in Oncology*, Vol. 24, No. 4, 1997, p S12-88), is respectfully traversed. With specific reference to claims 1-28 and 36-44, the rejection is rendered moot by the cancellation of these claims herein. With specific reference to claims 29-35 and 47, Applicants' invention, as defined for example by claim 29, distinguishes over Desai by requiring a method for the administration of a taxane to a subject in need thereof, the method comprising systemically administering a taxane to a subject in a formulation that may be safely administered using medical hardware made from materials containing extractable components. Desai does not disclose or suggest such a method.

In addition, it is respectfully submitted that Langer is not properly applied in combination with Desai, and is, in fact, irrelevant. As acknowledged by the Examiner (see Office Action mailed December 3, 2001, page 3, lines 1-3), Langer merely describes an infusion protocol of

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paclitaxel. Accordingly, it is respectfully submitted that Desai and Langer, either alone or in combination, do not disclose or suggest the present invention as defined by claims 29-35 and 47.

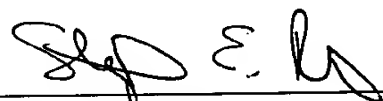
Applicants respectfully disagree with the Examiner's assertion that Applicants are not entitled to claim priority to parent application no. 60/051,021. The inventors of '021 are also inventors on the present application (which also acknowledges the inventive contributions of additional inventors). Clearly, the original inventors of '021 are entitled to claim priority to the provisional application which provides an early description of the claimed subject matter.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) are respectfully requested.

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. If any matters remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at the telephone number set forth below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Appendix

APPENDIX

29. (Amended) A method for the administration of a taxane [paclitaxel] to a subject in need thereof, said method comprising systemically administering said taxane [paclitaxel] to said subject in a formulation that may be safely administered using medical hardware made from materials containing extractable components.

30. (Reiterated) A method according to claim 29, wherein said medical hardware is selected from the group consisting of tubing, catheters, infusion bags, bottles, and syringes.

31. (Amended) A method for the administration of a taxane [paclitaxel] to a subject in need thereof, said method comprising systemically administering said taxane to said subject in a formulation that may be safely administered without the use of an in-line filter.

32. (Amended) A method for the administration of a taxane [paclitaxel] to a subject in need thereof, said method comprising systemically administering a complete dose of said [paclitaxel] taxane to said subject in a volume of less than 250 ml.

33. (Reiterated) A method according to claim 32, wherein said volume is less than 150 ml.

34. (Reiterated) A method according to claim 32, wherein said volume is less than 60 ml.

35. (Amended) A method for the administration of a taxane [paclitaxel] to a human subject in need thereof, said method comprising systemically administering said taxane [paclitaxel] to said subject at a rate [of at least 50 mg/m<sup>2</sup>/hour] between 6-30 mg/m<sup>2</sup>/min over an administration period of one hour or less.

46. (Amended) A [lyophilized] dry powder formulation [of paclitaxel] suitable for administration of [paclitaxel] a taxane to a human subject in need thereof upon reconstitution, wherein said formulation comprises taxane nanoparticles having a mean particle size in the range of about 10 nm up to about 8  $\mu$ m, wherein said formulation is substantially free of surfactant.

47. (Amended) A [reconstituted] formulation [of paclitaxel suitable for administration of paclitaxel to a subject in need thereof, said formulation comprising the lyophilized formulation of claim 41 and water or an aqueous solution] according to claim 46 wherein said formulation is lyophilized.

48. (Amended) A frozen formulation of [paclitaxel] a taxane suitable for administration of a taxane [paclitaxel] to a subject in need thereof upon thawing.

49. (Amended) A liquid formulation of a taxane [paclitaxel] suitable for administration to a human subject, said formulation comprising water and a taxane at a concentration of at least 2.0 mg/ml, wherein said formulation is stable for at least 3 days.

50. (Amended) A liquid formulation of a taxane [paclitaxel] according to claim 49, wherein said taxane [paclitaxel] concentration is at least 5.0 mg/ml.

51. (Amended) A liquid formulation of a taxane [paclitaxel] according to claim 49, wherein said taxane [paclitaxel] concentration is at least 10.0 mg/ml.

52. (Amended) A drug formulation suitable for administration of drug to a subject in need thereof by inhalation or oral administration, said formulation comprising [protein microparticles having a size of about 1-10  $\mu$ m, wherein said protein microparticles comprise] at least one protein and drug nanoparticles having a size of about [50] 10-1,000 nm, plus optionally an excipient.

53. (Reiterated) A method of making nanoparticles containing an active agent, said method comprising:

- a) combining a non-volatile phase, a volatile phase, and a surfactant that spontaneously form a microemulsion, wherein said volatile phase contains said active agent; and
- b) removing said volatile phase and thereby obtaining a suspension of solid nanoparticles in said non-volatile phase, wherein said nanoparticles contain said active agent and have an average diameter of less than 100 nm.

54. (Reiterated) A method according to claim 53, wherein said nanoparticles have an average diameter of less than 50 nm.

55. (Reiterated) A method according to claim 53, wherein said microemulsion further comprises a cosurfactant.

56. (Reiterated) A method according to claim 53, further comprising:

- c) removing said surfactant and/or cosurfactant by dialysis, ultrafiltration, or adsorption.

57. (Reiterated) A method according to claim 53, further comprising:

- c) removing essentially all of the remaining non-volatile phase by freeze-drying, spray-drying, or lyophilization, so as to obtain a dry powder of nanoparticles.

58. (Reiterated) A method according to claim 57, further comprising:

d) resuspending said dry powder of nanoparticles in a pharmaceutically acceptable carrier.

59. (Reiterated) A method according to claim 58, further comprising:

e) administering said resuspended nanoparticles to a patient.

60. (Reiterated) A method according to claim 53, further comprising:

c) filtering said suspension of solid nanoparticles through a filter of sufficiently small pore size so as to sterilize said suspension.

61. (Reiterated) A method of making nanoparticles containing an active agent, said method comprising:

a) combining a non-volatile phase and a volatile phase that spontaneously form a microemulsion, wherein said non-volatile phase contains said active agent; and

b) removing said non-volatile phase and thereby obtaining solid nanoparticles in said volatile phase, wherein said nanoparticles contain said active agent and have an average diameter of less than 100 nm.

62. (Reiterated) A suspension of nanoparticles made by the method of claim 53.

63. (Reiterated) Dry nanoparticles made by the method of claim 57.

64. (Reiterated) A suspension of nanoparticles made by the method of claim 58.

65. (Reiterated) A suspension of nanoparticles made by the method of claim 61.

66. (New) A dry powder formulation of a taxane suitable for administration of a taxane to a subject in need thereof upon reconstitution, wherein said formulation is substantially free of surfactants.

67. (New) A dry powder formulation of a taxane suitable for administration of a taxane to a subject in need thereof upon reconstitution, wherein said formulation is substantially free of cremophor.

68. (New) A formulation of a taxane suitable for administration of a taxane to a subject in need thereof, wherein said formulation comprises taxane nanoparticles having an average diameter in the range of about 10 nm up to about 8  $\mu$ m.

69. (New) A formulation according to claim 68, wherein said taxane nanoparticles are suitable for administration to a subject by oral, topical, ocular, intramuscular, intravenous, intraperitoneal, intraarterial, intraurethral, intrathecal, or inhalation administration.

70. (New) A lyophilized formulation suitable for administration of a taxane to a subject upon reconstitution, wherein said formulation comprises taxane nanoparticles whose size remains substantially constant prior to and after reconstitution.

71. (New) An article of manufacture comprising a sealed vial containing a dry powder formulation of a taxane, wherein said formulation comprises taxane nanoparticles having an average diameter in the range of about 10 nm up to about 8  $\mu$ m.

72. (New) An article of manufacture according to claim 74, wherein said formulation is stable for at least 3 days.



73. (New) An article of manufacture comprising a dry powder or liquid formulation of drug and at least one protein, wherein said formulation comprises drug nanoparticles that have been filtered through a sterilizing filter.

74. (New) An article of manufacture according to claim 73 wherein said drug is a taxane.

75. (New) An article of manufacture according to claim 73 wherein said liquid formulation of taxane is free of surfactants

76. (New) The method of claim 35 wherein said rate is between 6-16 mg/m<sup>2</sup>/min.

77. (New) The method of claim 35 wherein said taxane is used to treat cancer in said human subject.

78. (New) The method of claim 35 wherein said taxane is used to treat vascular restenosis in said human subject.

79. (New) The composition of claim 46 wherein said nonoparticles have a mean particle size in the range of about 29 nm up to about 400 nm.

80. (New) The composition of claim 46 wherein said dry powder formulation of taxane is suitable for the treatment of tumors in the brain or peritoneal cavity.

81. (New) A liquid formulation of a taxane according to claim 49, wherein said taxane concentration is at least 20 mg/ml.

82. (New) A method for the administration of a taxane to a human subject in need thereof, said method comprising systemically administering said taxane to said subject at a concentration of at least 2 mg/ml.

83. (New) The method of claim 82 wherein said concentration of said taxane is at least 5 mg/ml.

84. (New) The method of claim 82 wherein said concentration of said taxane is at least 10 mg/ml.

85. (New) The method of claim 82 wherein said concentration of said taxane is at least 20 mg/ml.

86. (New) A drug formulation according to claim 52 wherein said drug nanoparticles are contained within protein microparticles having a size of about 1-10  $\mu\text{m}$ .

87. (New) The formulation of claim 52 wherein said drug formulation may be used in conjunction with oral bioavailability enhancers.

88. (New) An article of manufacture comprising a drug formulation in a sealed vial suitable for administration of a drug to a human subject in need thereof, said formulation comprising at least one protein and drug nanoparticles having a size in the range of about 10 nm up to about 1000 nm.

89. (New) The composition of claim 88 wherein said drug formulation is a dry powder.

90. (New) The composition of claim 88 wherein the drug formulation is a liquid.

91. (New) The composition of claim 88 wherein said drug is hydrophobic.
92. (New) A formulation of paclitaxel suitable for administration to a human subject in need thereof wherein the pharmacokinetics are such that the area under the curve (AUC) for paclitaxel in said formulation is significantly less than the AUC for paclitaxel in TAXOL at the same dose.
93. (New) A formulation of paclitaxel suitable for administration to a human subject in need thereof wherein the pharmacokinetics are such that half-life for paclitaxel in said formulation is significantly higher than the half-life for paclitaxel in TAXOL at the same dose.